Application/Control Number: 09/944,564
Art Unit: 1623

USPTO
Examiner Patrick T. Lewis, PhD
Fax Number: 001-703-872-9306

BY TELEFAX – 5 pages + table of comparison (page 6)+ covering letter and Filing Receipt

August 4, 2004

Response to Detailed Office Action dated May 5, 2004

Dear Examiner,

In response to the above-identified Office Action , please find herewith a response regarding Election/Restriction of the invention. Results of statistical analysis of the clinical trial and annexes will be sent by mail.

Best regards.

Yours Sincerely,

N. Nassaim

Dr. Nida Nassief

OFFICIAL

Response to Office Action dated May 5, 2004.

Applicant's Response dated February 11, 2004

Page 2 of the Office Action:

No response.

Election/Restriction

Page 3 of the Office Action:

Invention 1 as identified by the examiner in the Detailed Office Action " a pharmaceutical composition consisting essentially of glycophosphopeptical and a method of treatment of allergy and asthma" **have been elected.**. This invention includes claims 25-27 inclusive.

The non-elected claims will be withdrawn. According to the Office Action, the other inventions described by the Examiner might be rejoined or I will have the right to file a Divisional Application.

Similarity of invention I and invention II

The relationship between the two active agents Glycophosphopeptical and Nigella sativa is based on disclosed commonality of the mode of operation, function and effect, rather than similarity of the active agent.

The invention as claimed has been limited to the use of the Th1 stimulating agents glycophosphopeptical and pure seeds of Nigella sativa in the manufacture of medicaments for the treatment and/or prophylaxis of asthma/allergy. They have similar therapeutic properties, utility of such

properties and uniqueness of the selected clinical and laboratory variables that were used to assess improvement after a course of treatment.

The nature and significance of the differences between the prior art and the claimed invention as clear from the table of comparison between glycophosphopeptical or/and Nigella sativa asthma medication and current asthma preventive therapy. It is very clear that the claimed subject matter will function in an equivalent manner (last page of the report.

Following are more detailed description of the totality of evidence in relation to the uniqueness of the invention and the mutually exclusive characteristics of the inventive approach for the treatment and/or prophylaxis of asthma/allergy with the two Th1 stimulating agents (glycophosphopeptical or seeds of Nigella sativa) that was perceived through the following observations:

1. The same unique onset of action, magnitude and pattern of changes in clinical assessment criteria
   during treatment with both agents.

2. The similarity in the laboratory main outcome of the clinical trials, in particular sputum eosinophils that are considered as the pharmacological target site.

3. A short-course 5-days treatment using either of the two agents resulted in the same unique long-
   term clinical remission term.

4. The similarity in the dosage and duration of the treatment that was effective to:

- Switch-off the airway eosinophilic inflammation.
- Reduce mucus secretion and as a mucolytic agent.
- Reduce symptom scores significantly.
- Restore airways patency as measured by a Pulmonary Function Test.

Such treatment is unknown and totally unexpected from the prior art. Statistical analysis of results of clinical trial will be sent by mail.

5. The most important and unique achievement is a corresponding permanent effect both for glycophosphopeptical and Nigella sativa has been experimentally verified, in respect of the treatment of allergic rhinosinusitis, by means of X-ray photographs of the paranasal sinuses of patients subjected to corresponding treatments.

Annex I shows copies of two X-ray photographs, the top one showing the paranasal sinuses of a patient suffering from allergic rhino-sinusitis who had previously undergone conventional therapy, but before the inventive treatment with glycophosphopeptical, and the bottom one is a corresponding X-ray after the inventive treatment. From the bottom photo it can be seen that the treatment led to very good resolution of the mucosal thickening of the right maxillary antrum, better aeration of the nasal cavity and mild-moderate resolution of the turbinate hypertrpophy.

Annex II shows copies of two X-ray photographs, the top one showing the paranasal sinuses of a patient suffering from chronic allergic rhinosinusitis and asthma who had previously undergone conventional therapy, but before the inventive treatment with Nigella sativa, and the bottom one is a corresponding X-ray after the inventive treatment. From the bottom photo it can be seen that the treatment led to good resolution of the mucosal thickening of the right and left maxillary antrum, better aeration of the nasal cavity and good resolution of the turbinate hypertrpophy

Annex III is a copy of a review article, published in 2003, regarding the treatment of allergic rhinitis by intranasal steroid sprays, which is regarded as the best conventional treatment. This article mentions only an improvement in patient symptoms. These conventional treatments do not lead to resolution of the mucosal thickening, as is produced by the inventive treatments, and seen in Annex I and Annex II, bottom photographs.

The inventive treatments with both glycophosphopetical and Nigella sativa are hence characterized by a common effect differentiating them from conventional treatments.

Newly-introduced Annex III attests that the best known treatment with corticosteroids merely provide symptomatic relief.

Unity of Invention

Each of the aspects of the invention – Th1 stimulating agent selected from glycophosphopeptical and Nigella sativa seeds – thus provides a common contribution over the state of the art, when considered in the overall context of the claims.

In actual fact, the development of the whole invention and the linked hypothesis occurred as a single jigsaw puzzle, the different parts were placed one-by-one to form a masterpiece that resolves an international enigma! Without the guiding lights of each step it is rather impossible to complete the whole masterpiece. This is the factor underlies the success of my invention to produce a successful treatment for a chronic disabling disease (as considered by the FDA) when others fail; I find it rather difficult to cut it into pieces and bits!

This **common contribution** could be expressed in an additional claim :

> Use of a Th1 stimulating agent selected from glycophosphopeptical and pure seeds of Nigella sativa in the manufacture of a medicament for the treatment and/or prophylaxis of asthma/allergy in a mammal such as a human, wherein the medicament is presented in a form for short term therapy by administration over a period 3 to 30 days, preferably over 5 days, to produce a long term clinical remission over a period of months.

Similarity of invention II and invention III, IV and V

Invention II and III are related as a product and process of use. Both are classified in the same class 424 in the Office Action. The process is not more

than a technique that that was used to define the invention.. In this product claim I have used a novel process as one of the criteria of the invention and one design for its use; the novel nonobvious product was used to obtain a novel end result.

If the Examiner will accept my argument above then the different uses of the allowed product claim will be rejoined in relation to invention III, IV and V in relation to invention II

The end of the report

nigella sativa

Table: Comparison between Nigellasativa (Glycophosphopeptical) asthma medication and current preventive asthma therapy that brings effective control of symptoms and spares oral steroid use

Drug	Duration of treatment	Onset of clinical response	% decrease in symptom score	Decrease in sputum eosinophils	Lowering of total serum IgE	Changes in mucus	Type of asthma	Prolonged effect
Nigellasativa (Glycophosphopeptical)	**5 DAYS ONLY Taken Orally**	**DAY 3**	**65-100%**	**70-90%**	**50% within 8 weeks**	**Decreased quantity and viscoelasticity**	**Intrinsic & allergic**	**YES**
Th2 inhibitor (Ref 1)	8 weeks or more oral	Week 3 &4	40%	—	Significant from baseline at week 4	—	Severe steroid dependancy	NO
Monoclonal anti-IgE (Ref 2 & 3)	21 weeks or more IV injection	Week 12	30% in daytime and night time symptom score (main outcome)	Increase following allergen challenge was attenuated	Within one hour day 0 (first dose complex). Return to base line within 4-5 half-lives of the drug.	—	Allergic only	NO
Cromolyn	Continuous 2 sprays QDS			Significant decrease in the responder group	Has been shown to reduce IgE synthesis (Ref 6).	—	Allergic only Mostly children	NO
Anti-Leukotrienes (Ref 4)	Continuous oral	Occurs within one day	Reduction from baseline in day-time asthma symptom score (-23%), night time awakening (-19%)	Peripheral blood eosinophils: Significant reduction over the 13-week treatment period		—		NO
Inhaled Corticosteroids Currently the 1st Line treatment Used widely for the past 10 years	Continuous for YEARS Daily multiple inhalations Many preparations available	Within 2 weeks	Currently most effective. Results according to prep used. 53% inc. in asthma control days, & 22% in nights without awakening	Peripheral blood eosinophils: 15% change from baseline	Systemic corticosteroids ENHANCE IgE synthesis, raising the concern that early administration of corticosteroids may enhance the development of atopy and asthma (ref 5)	Four weeks treatment with low-dose beclomethasone dipropionate was NOT associated with large reductions in markers of eosinophilic inflammation, broncho-vascular permeability, or mucus hypersecretion (Ref 5).	Intrinsic & allergic	NO
Immunotherapy	Optimal duration unknown, 3-5 years for patients who have had a good therapeutic response Weekly injection Serious side effects		The combined odds of symptomatic improvement was 3-2 (95% CI 2.2-4.9) Using mixture of allergen in unselected asthma showed NO significant difference from placebo (Ref 7).	Inhibit immediate release of mast cell mediators and eosinophil number in nasal lavage in response to allergen provocation.	Serum allergen-specific IgE concentrations initially rise and then gradually fall to baseline levels over months, total serum IgE increase. Oligonucleotide therapy leads to a reduced specific IgE		Allergic only	YES 3-5 years therapy resulted in prolonged effect up to 3 years.

Ref 1: Tamaoki J., et al. Effect of suplatast tosilate, a Th2 cytokine inhibitor, on steroid-dependant asthma. The Lancet 2000, July 22 ; 536: 273-8.
Ref 2 : Milgrom H., et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. The New Eng J of Med 1999, Dec 23; 341(26): 1966-1973.
Ref 3: Fahy J. V. Reducing IgE levels as a strategy for the treatment of asthma. Clin Exp Allergy 2000; 30 (Suppl 1): 16-21.
Ref 4: Robert a., et al. Zafirlukast improves asthma symptoms and quality of life in patients with moderate reversible airway flow obstruction. J Allergy Clin Immunol 1998 Dec: 102 (6 part 1): 935-941.
Ref 5: Fahy-JV, Boushey-HA. Effect of low-dose beclomethasone dipropionate on asthma control and airway inflammation. Eur-Respir-J 1998 June; 11 (6); 1240-7.
Ref 6: Peter Van Asperen. Can asthma be prevented? Emirate Medical Journal 1998; 17 (2): 107-108.
Ref 7: WHO position paper, Allergen Immunotherapy: therapeutic vaccines for allergic diseases. Allergy 1998; 53 (44 suppl) :17.

Office Action Summary	Application No.	Applicant(s)
	09/944,564	NASSIEF, NIDA ABDUL-GHANI
	Examiner	Art Unit
	Patrick T. Lewis	1623

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION. R-112

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *25-34* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.